# SOCIOECONOMIC STATUS, CEREBELLAR STRUCTURE, AND EXECUTIVE FUNCTIONS IN CHILDREN AND ADOLESCENTS WITH SPINA BIFIDA MYELOMENINGOCELE

_____

A Thesis

Presented to

The Faculty of the Department

of Psychology

University of Houston

_____

In Partial Fulfillment

Of the Requirements for the Degree of

Master of Arts

_____

By

Brian Biekman

August, 2019

# SOCIOECONOMIC STATUS, CEREBELLAR STRUCTURE, AND EXECUTIVE FUNCTIONS IN CHILDREN AND ADOLESCENTS WITH SPINA BIFIDA MYELOMENINGOCELE

_____

An Abstract of a Thesis

Presented to

The Faculty of the Department

of Psychology

University of Houston

_____

In Partial Fulfillment

Of the Requirements for the Degree of

Master of Arts

_____

By

Brian Biekman

August, 2019

## ABSTRACT

Spina bifida myelomeningocele (SBM) is a congenital neurological defect associated with abnormal cerebellar structure and poorer executive functions (EFs) in children. This study investigated the impact of cerebellar volume on EFs in children with SBM and the potential moderating effect of socioeconomic status (SES). 25 typically developing (TD) children and 74 children with SBM underwent a structural MRI, which was used to measure the volumes of three cerebellar regions: the anterior lobe, posterior lobe, and corpus medullare. A parent-report questionnaire was administered which measured two major EF constructs: metacognition and behavioral regulation. We hypothesized that a larger posterior lobe and corpus medullare would predict greater EFs in both constructs, and that this prediction would be larger in children with SBM. We also hypothesized that, for children with SBM, this prediction would be larger in children with lower SES. Multivariate multiple regression analyses found that the combination of the EF constructs was predicted by group (trace=.122, p=.003) and age (trace=.114, p=.005), such that parents of younger children and children with SBM reported worse EFs. Specifically, group predicted metacognition (β=1.33, 95% CI: [40, 2.25], p=.005) and behavioral regulation at the trend level (β=.92, 95% CI: [-.07, 1.89], p=.07), and age predicted behavioral regulation (β=-.31, 95% CI: [-.51, -.10], p=.004). For children with SBM, age predicted the combination of the constructs (trace=.107, p=.03), and specifically predicted behavioral regulation (β=-.29, 95% CI: [-.55, -.03], p=.03). However, no cerebellum volume measurement significantly predicted either EF construct. The group x volume and group x SES interactions were also non-significant. Therefore, the question of the impact of cerebellar volume on EFs in SBM remains inconclusive.

## TABLE OF CONTENTS

Introduction..... 1

Subtypes of spina bifida..... 2

Spina bifida occulta..... 2

Spina bifida meningocele..... 2

Spina bifida myelomeningocele..... 2

Spina bifida lipomeningocele and lipomyelomeningocele..... 3

Prenatal development of spina bifida myelomeningocele..... 3

Primary neurological insults caused by SBM..... 4

Spinal cord damage..... 4

Chiari II malformation..... 4

Cerebellar differences in SBM..... 5

Corpus callosum dysgenesis..... 6

Secondary neurological insults caused by SBM..... 6

Hydrocephalus..... 6

Corpus callosum hypoplasia..... 7

Executive Functions..... 7

Executive Functions in SBM..... 9

Neuroscience of executive functions—the role of the cerebellum..... 11

Socioeconomic status and executive functions..... 15

Socioeconomic status and executive functions in SBM..... 16

Socioeconomic status as a potential moderator of brain-EF relationships in SBM..... 18

Aims..... 18

Method..... 19

Participants..... 19

Measures..... 20

Socioeconomic status..... 20

Executive Functions..... 21

MRI Analysis..... 22

Image Acquisition..... 22

Brain Segmentation and Parcellation..... 23

Hypotheses..... 24

Statistical Methods..... 26

Results..... 28

Discussion..... 33

References..... 39

## LIST OF TABLES

Table 1. Test of the full Multivariate model, including joint prediction of BRIEF Behavioral Regulation and Metacognition index..... 28

Table 2: Multivariate multiple regression model with regression weights, 95% confidence intervals, p values, and relative importance (i.e., R2) of the predictors..... 29

Figure 1: Q-Q plot of multivariate outliers for Aim 1..... 30

Table 3: Test of joint prediction of Behavioral Regulation and Metacognition indices (SBM group only)..... 31

Table 4: Multivariate multiple regression model with regression weights, 95% confidence intervals, p values, and relative importance (i.e., $R^2$) of the predictors (SBM group only)... 32

Figure 2: Q-Q plot of multivariate outliers for Aim 2..... 33

## Introduction

Spina bifida is a congenital neurological defect in which the vertebral column fails to fully cover the spinal cord. Spina bifida myelomeningocele (SBM) is the most debilitating type of spina bifida and the most common debilitating congenital defect after heart disease. The majority of SBM births are associated with hydrocephalus and require shunting to prevent serious injury or death from high intracranial pressure (Copp, Adzick, Chitty, Fletcher, Holmbeck, & Shaw, 2015). SBM causes many primary and secondary neural insults that result in atypical neural development. Some of these insults, including the Chiari II malformation, substantially and negatively impact the structural integrity of the cerebellum. SBM is also associated with a pattern of cognitive deficits and assets: the cognitive phenotype (Dennis & Barnes, 2010). One of the most important aspects of cognition—in SBM and in typically developing populations—is executive functions (EFs). The cerebellum, initially believed to primarily serve fine motor function and timing, is now recognized as an important region in executive functioning. Environmental factors have a major impact on executive functioning in SBM and typical development. One of these factors is socioeconomic status (SES). This paper addresses the possible relationship between the cerebellum and EFs in SBM and the possible moderation of SES.

## Subtypes of spina bifida

### *Spina bifida occulta*

Spina bifida occulta is a common (10-20% of live births), extremely mild defect in which a slight malformation of one or more vertebrae fails to completely cover the spinal cord (Boone, Parsons, Lachmann, & Sherwood, 1985; Copp et al., 2015). All layers of the skin and muscle that cover the vertebrae are intact. Spina is usually asymptomatic and is rarely associated with any negative outcomes (Boone et al., 1985; Copp et al., 2015). Studies of neuropsychological correlates of spina bifida are almost never concerned with occulta; I briefly discuss this subtype of spina bifida because it shares the same descriptor as the other subtypes of spina bifida that *are* associated with negative outcomes.

### *Spina bifida meningocele*

In spina bifida meningocele, one or more vertebrae completely fail to cover the spinal cord and a small section of the meninges (i.e. a lesion) containing cerebrospinal fluid (CSF), protrudes from the back (Copp et al., 2015). The lesion does not contain the spinal cord.

### *Spina bifida myelomeningocele*

Spina bifida myelomeningocele (SBM; also called spina bifida meningomyelocele) is the most common subtype of spina bifida after occulta. SBM is similar to spina bifida meningocele except the lesion also contains part of the spinal cord. Furthermore, the lesion is often fully exposed to the outside environment. SBM is one of the most common debilitating congenital defects with incidences that vary widely across countries (0.5-10 cases per 1,000

pregnancies, Greene & Copp, 2014). For the rest of this paper, when I use the term spina bifida, I am referring to spina bifida myelomeningocele, unless I state otherwise.

*Spina bifida lipomeningocele and lipomyelomeningocele*

These subtypes of spina bifida are similar to meningocele and myelomeningocele, respectively, except the lesions are also filled with a lipoma (i.e. a fatty lump). These subtypes are extremely rare and will not be discussed further in this article.

## Prenatal development of spina bifida myelomeningocele

Myelomeningocele forms during a small window of embryonic development: between 22 and 26 days after fertilization, during the process called primary neurulation (Copp et al., 2015; Greene & Copp, 2014). At the beginning of primary neurulation, embryonic cells are arranged into three layers. The top layer is the ectoderm with the mesoderm underneath and the endoderm underneath the mesoderm. Cells in a segment of the ectoderm, the neural plate, begin to dive towards the mesoderm in a folding pattern, creating the neural groove. Finally, the two ends of the neural groove fuse with each other, creating the neural tube (Bassuk & Kibar, 2009). A completely closed neural tube is vitally important as it allows the central nervous system to develop without interference from the surrounding environment.

Closure of the neural tube initiates in several places (Nakatsu, Uwabe, & Shiota, 2000). The neural tube closure relevant to myelomeningocele begins at the bottom of what will become the sacral spine and at intersection of the future hindbrain and future cervical spine. The former “zips up” and the latter “zips down” until they meet in the lumbosacral region (Copp et al., 2015). Arrest of this “zipping” procedure is myelomeningocele and most

commonly occurs at the lumbosacral level but sometimes occurs at the thoracic level. Children with these "upper-level" thoracic lesions, have lower IQs, academic achievement, and adaptive behavior, with a higher rate of intellectual disability (Fletcher et al., 2005) as well as lower cognitive and executive functioning than children with "lower-level" lumbosacral lesions (Wasserman & Holmbeck, 2016).

## Primary neurological insults caused by SBM

### *Spinal cord damage*

In myelomeningocele, cells that will eventually form the spinal cord at the level of the lesion are perpetually exposed to amniotic fluid until birth. These cells initially undergo normal development. However, amniotic fluid is toxic to these cells and, progressively, some of these cells hemorrhage and die (Copp et al., 2015). This leads to poor muscle function below the level of the spinal lesion, including issues with ambulation and bladder and bowel control.

### *Chiari II malformation*

A neurological insult found almost universally and exclusively in SBM, the Chiari II malformation, occurs when the inferior cerebellar vermis and the brainstem are displaced downward through the foramen magnum and into the cervical spinal cord. The dominant paradigm in understanding the cause and development of the Chiari II malformation is the "unified theory" (Juranek & Salman, 2010). During normal embryonic development, there is a temporary period of "spinal neurocele occlusion" where the ventricular and spinal cavities become a closed system. Simultaneously, different processes like CSF production place

pressure on this closed system, causing distension (i.e. expansion) of the system. This causes the expansion of what becomes the posterior fossa. Because the neural tube fails to close in SBM, spinal neurocele occlusion fails to occur. This causes an abnormal distension of the system and, subsequently, an abnormally small posterior fossa. In healthy populations as well as those with SBM, the cerebellum rests on and is partly shaped by the posterior fossa. A small posterior fossa causes the cerebellum to be compressed (with possible herniation), causing it to bend around the brainstem, be displaced upwards, downwards through the foramen magnum. “Tectal beaking”, in which the superior and inferior colliculi fuse and protrude posteriorly towards the cerebellum, is another prominent neurological insult caused by the Chari II malformation (Copp et al., 2015). Additional neurological consequences of the Chiari II malformation include aqueductal stenosis, a smaller and inferiorly displaced fourth ventricle, a larger tentorium incisura, and heterotopias (for more information, read Juranek & Salman, 2010 and Stevenson, 2004).

Cerebellar Differences in SBM

Another prominent feature of the Chiari II malformation is altered cerebellar volume. Reduction in gross cerebellar volume forms early in gestation, as early as 16 weeks in one case (Brocklehurst, 1969). However, cerebellar volume is not uniformly reduced in SBM. Fletcher and colleagues found reduced volume in lateral cerebellar hemispheres but unchanged volume in the medial cerebellum (Fletcher, Copeland, Fredrick, Blaser, Kramer et al., 2005). Other studies have found a pattern of reduced posterior lobe volume and increased anterior lobe volume (Dennis, Salman, Juranek, & Fletcher, 2010; Juranek, Dennis, Cirino, El-Messidi, & Fletcher, 2010).

*Corpus callosum dysgenesis*

Another primary neurological insult of SBM is corpus callosum (CC) dysgenesis, also called partial agenesis or hypogenesis, in which parts of the CC—or more rarely, the entire CC—fails to form. Although the mechanisms of CC dysgenesis are not as well known as the mechanisms of the Chiari II malformation, it is thought to be caused by disruptions in the normal CC development that occurs 7-20 weeks post-fertilization (Hannay, 2000; Hannay, Dennis, Kramer, Blaser, & Fletcher, 2009; Juranek & Salman, 2010). There is rarely complete callosal agenesis in SBM. More often, there is a pattern of formed and unformed CC subsegments. The rostrum and splenium are most often missing in cases of callosal dysgenesis (Hannay, 2000).

## Secondary neurological insults caused SBM

*Hydrocephalus*

A prominent secondary CNS insult, caused by the Chiari II malformation, is hydrocephalus. Hydrocephalus is an excess buildup of cerebrospinal fluid (CSF) in the ventricular system with poor or nonexistent pathways to circulate CSF out of the brain. The downward displacement of the cerebellum and brain stem, found in the Chiari II malformation, blocks the cerebral aqueduct, the primary pathway for CSF circulation out of the brain. Despite this, CSF production in the choroid plexus continues and places pressure on the ventricles. The lateral ventricles expand to an abnormal size and intracranial pressure (ICP) will increase. Increased ICP can shift brain structures, especially at the midline, and

stretch, shear, and destroy axons. Over the lifespan, 90% of people with SBM will have enlarged ventricles and 50-80% will require surgical intervention for hydrocephalus. In most cases of SBM, hydrocephalus is treated with diversionary shunting. In less common cases, hydrocephalus stabilizes with a manageable intracranial pressure (i.e. arrested hydrocephalus; Schick & Matson, 1961). In even rarer cases, there is no hydrocephalus.

*Corpus callosum hypoplasia*

As mentioned before, the increased ICP caused by hydrocephalus can stretch, damage, or destroy axons—especially the axons closest to the lateral ventricles. This is most prominent in the corpus callosum, which is directly adjacent to the lateral ventricles. In addition to dysgenesis of the corpus callosum that is a primary neurological insult of SBM, the secondary insult of hydrocephalus causes a less voluminous corpus callosum with weakened structural integrity (Bradley, Juranek, Romanowksa-Pawliczek, Hannay, Cirino et al., 2016).

## Executive functions

Executive functions (EFs) are a family of deliberate, controlled cognitive processes used to complete a task "when going on automatic or relying on instinct or intuition would be ill-advised, insufficient, or impossible" (Diamond, 2013). Neuropsychology literature has identified three core EFs: inhibitory control, working memory, and cognitive flexibility (Diamond, 2013; Lehto, Juujarvi, Kooistra, & Pulkkinen, 2003; Miyake, Friedman, Emerson, Howerter, & Wager, 2000). Inhibitory control (also called impulse control, response inhibition, attentional control, selective attention, and executive attention, among other terms) involves avoiding an action or behavior that is intrinsically or extrinsically more

appealing, but irrelevant or counter-productive to the task at hand. Processes like suppressing a prepotent response in favor of the correct response on (e.g. Stop-Signal task; Verbruggen & Logan, 2008), or refraining from interrupting others (Gioia, Isquith, Guy, & Kenworthy, 2000), rely on inhibitory control.

Working memory involves holding information in short-term memory and manipulating that information to complete a task. Neuropsychological literature often separates working memory, into a verbal component and a visuospatial component (Baddeley & Hitch, 1994). Some neuropsychologists further separate visuospatial working memory into visual and spatial components (Mammarella, Cornoldi, & Donadello, 2003).

Cognitive flexibility (also termed set-shifting and task-switching) involves being able to change one's actions based on changed task demands. Children with poor cognitive flexibility have difficulties understanding the changes in rules and, behaviorally, often have difficulties adjusting to changes in routine or encountering new situations (Gioia et al., 2000). Although these core EFs are dissociable, they often support each other. Moreover, these core EFs build more complex EFs such as planning, problem solving, behavioral regulation, and metacognition (Diamond, 2013).

Variability in EFs are associated with numerous mental and physical health outcomes in children. In a longitudinal study that assessed children in early to middle childhood and followed them into their 30s, poor self-control in childhood predicted more physical health issues, more substance dependence issues, less wealth, and greater incidence of raising a child as a single parent. Furthermore, poor self-control in childhood predicted whether one would be convicted of a crime as an adult better than low IQ or low family-SES in childhood.

However, these effect sizes were small at best and were slightly weakened when controlling for IQ and social class (Moffitt, Arseneault, Belsky, Dickson, Hancox et al., 2011).

EFs are also important for academic achievement. Self-regulation before kindergarten has been found to correlate with development of math, verbal, and reading skills in kindergarten and the year following kindergarten, with small to medium effect sizes (Blair & Razza, 2007; Hubert, Philippe, Florin, & Tracy, 2015).

## Executive functions in SBM

As in typically developing populations, the development of EFs in children and adolescents with SBM are predictive of critical functional outcomes. Zukerman and colleagues administered an informant-reported questionnaire of global executive functioning and a performance measure of initiation, planning, sustained attention, and problem-solving in early adolescents with SBM and age-matched TD controls. They modeled these measures onto life milestones in late adolescence/early adulthood. Global EFs predicted the likelihoods of moving away from home, history of a romantic relationship, and the number of close friends while the performance measure predicted college attendance. Group-by-EF interactions were negligible, suggesting that the relationship between EFs in adolescence and young adult life outcomes in SBM closely resembled that of TD children (Zukerman, Devine, & Holmbeck, 2010). Specific to SBM, adherence to a medical regimen (e.g. bowel regimen, catheterization) and autonomy in carrying out those regimens were moderately predicted by global EF (O'Hara & Holmbeck, 2013). Recognizing the substantial executive component in daily living, Jacobson and colleagues designed a questionnaire that emphasized executive functioning in abilities to self-care (Jacobson, Tarazi, McCurdy, Schultz, Levey et

al., 2013). Other studies have found that EFs mediate the relationship between group (SBM vs. typically developing) and social problem-solving skills (Landry, Taylor, Swank, Barnes, & Juranek, 2013), the relationship between group and social adjustment (Rose & Holmbeck, 2007), and the relationship between severity of neurological insult and impairments to functional independence (Heffelfinger, Koop, Fastenau, Brei, Conant et al., 2008). EFs are also related to psychopathology in SBM: greater executive dysfunction was significantly related to greater self-reported and parent-reported internalizing symptoms (Lennon, Klages, Amaro, Murray, & Holmbeck, 2014). Similarly, Kelly and colleagues found that children with SBM had higher rates of internalizing symptoms than TD children and that metacognitive function mediated that relationship (Kelly, Ammerman, Rausch, Ris, Yeates et al., 2012).

In studies comparing pediatric SBM and typically developing groups on executive functions, the SBM group has shown greater global EF dysfunction on a teacher-reported and parent-reported questionnaire (Gioia et al., 2000; Zukerman et al., 2010), and greater working memory dysfunction measured by the same questionnaire (Rose & Holmbeck, 2007). In another study that used that questionnaire, children with SBM had greater executive dysfunction than typically developing children with respect to initiation ($\eta_p^2 = .14$), working memory ($\eta_p^2 = .14$), planning/organization ($\eta_p^2 = .09$), and organization of materials ($\eta_p^2 = .07$), with medium to large effect sizes. Behavioral regulation differences were nonsignificant with an unreported effect size. Furthermore, the metacognitive dysfunction of children with SBM was moderately more likely to be clinically significant (i.e. above 95% percentile of published norms; odds ratio = 5.93), and behavioral regulation dysfunction was

slightly more likely to be clinically significant (odds ratio = 2.49; Brown, Ris, Beebe, Ammerman, Oppenheimer, et al., 2008).

## Neuroscience of executive functions—the role of the cerebellum

Neuroscience research of executive functions has identified a central executive network (also called the executive control network) that consists of the prefrontal cortex, posterior parietal cortex, and basal ganglia (Dennis, Simic, Bigler, Abildskov, Agostino et al., 2013). Although studies of this network in healthy controls massively outnumber studies of this network in SBM, some studies suggest that these regions subserve EFs in SBM as well. In a sample of children with SBM from this dataset, variability in gray matter structural integrity for three basal ganglia regions (thalamus, putamen, and globus pallidus) were correlated with metacognition and behavioral regulation. Surprisingly, thickness of the dorsolateral prefrontal cortex was not significantly correlated with metacognition or behavioral regulation (Ware, Kulesz, Williams, Juranek, Cirino, & Fletcher, 2016).

In the last two decades, the cerebellum, long believed to primarily serve as the hub of fine motor control, coordination, and learning, has been theorized and empirically supported as a component of the central executive network (Bostan, Dum, & Strick, 2013). Functional connectivity studies have found that the cerebellar neurons share a functional relationship with various neural networks, including the executive control network (Habas, Kamdar, Nguyen, Prater, Beckmann et al., 2009; O'Reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2010). Task-based fMRI studies in healthy controls have found cerebellar—and concurrent prefrontal and posterior parietal—activation during nonverbal auditory working memory tasks (Salmi, Pallesen, Neuvonen, Brattico, Korvenoja et al., 2010).

In the last decade, research has begun to establish which regions of the cerebellum are associated with which functions. In one functional connectivity study, O'Reilly and colleagues divided the cerebellum into the primary sensorimotor zone (lobules V, VI, and VIII), which serves perceptual and motor functions, and the supramodal zone (lobule VIIa and crus I and II), which was functionally connected to the posterior parietal lobe and prefrontal cortex (O'Reilly et al., 2009). Habas and colleagues similarly divided the cerebellum into the the right and left executive control networks (containing crus I and II), the salience network (lobule VI), the default-mode network (lobule IX; Habas et al., 2009). Salmi and colleagues used task-based fMRI and diffusion weighted MRI to multimodally examine the functions of the different cerebellar regions. Load increase in an auditory working memory task was associated with increased activity in lobules VII and VIII of the posterior cerebellum as well as areas of the central executive network. Activity in crus I and II was positively associated with optimization of response speed on the auditory working memory task. On the other hand, a sensory-motor control task was associated with increased activity in lobules V and VI of the anterior cerebellum. These regions did not show increased activation with load increase in the auditory working memory task. Diffusion-weighted imaging tractography showed that crus I and II was linked to the same prefrontal areas activated in the auditory working memory task but that the anterior lobe was not connected to those areas (Salmi et al., 2010).

Neuropsychological studies of abnormal cerebellar structure have often found associated executive functioning deficits. Adults with cerebellar atrophy evidenced planning deficits (Grafman, Litvan, Massaquoi, Stewart, Sirigu et al., 1992). A sample of adults with ischemic and surgical lesions in the cerebellum showed deficits in response inhibition and monitoring

(Brunamonti, Chiricozzi, Clausi, Olivito, Giusti et al., 2014). Deficits in problem solving, abstract thinking, and set shifting, have been found in adults with cerebellar damage (Mak, Tyburski, Madany, Sokołowski, & Samochowiec, 2016) and children and young adults with malignant cerebellar tumors (Karatekin, Lazareff, Asarnow, 2000). However, these studies have limited generalizability to SBM because these participants had an acquired cerebellar insult—for them, the cerebellum developed normally before the insult. In contrast, the cerebellum of children with SBM has always developed abnormally from gestation to the time of assessment and MRI. The cerebellar insult is developmental, not acquired.

Studies of the cerebellum and cognition in SBM are rare. In one study, lower cerebellar white matter volume was correlated with more errors in verb generation in SBM, with a medium effect size ($r = -.39$; Dennis, Jewell, Hetherington, Burton, Brandt et al., 2008). The correlation between cerebellar gray matter volume and verb generation performance was not significant. In a study that was nonspecific to the cerebellum, Vinck and colleagues found that presence of the Chiari II malformation was associated with poorer visual analysis and synthesis, verbal memory, and verbal fluency in children. However, whether these behavioral problems are due to cerebellar insult/lack of development or other secondary effects of SBM (i.e. hydrocephalus and/or other neural insults of the Chiari II malformation) are unclear (Vinck, Maasen, Mullaart, & Rotteveel, 2006).

The presence or absence of associations between cerebellar structure and executive functioning in SBM could be explained by several neurocognitive processes. The first possibility is that cerebellar insults that characterize SBM such as the Chiari II malformation may hinder the development of cerebellar projections to other regions of the central executive network. If so, finding that smaller cerebellar volume is associated with greater

executive dysfunction may reflect a weakened central executive network due to damaged cerebellar projections and an inability of the cerebellum to fully perform its role in EFs. A second possibility is that SBM could dramatically reorganize the cerebellum such that regions that are associated with motor and cognitive functions in TD children are different for children with SBM. A third possibility is that the cerebellar insults of SBM could completely prevent the formation of projections to the executive control network or the cerebellar projections could form but become severed in utero or in infancy or early childhood. Finding a negligible relationship between cerebellar volume and executive dysfunction could reflect the second or third possibility although many more studies with similar findings would be necessary to reach such a conclusion. With respect to the third possibility, it is possible, but unlikely, that there are no cerebellar projections to the central executive network in SBM.

The complete white matter pathway from the cerebellum to the prefrontal lobes has not been studied in SBM. However, white matter tracts that pass through the cerebellum, including two cerebellar structures thought to be related to EFs, the dentate nucleus and superior cerebellar peduncle (Salmi et al., 2010), have been studied in children with SBM. Although these tracts often have lower structural integrity, they are typically still present (Meoded, Bosemani, Boltshauser, Scheer, Huisman, & Poretti, 2017). Therefore, we would not hypothesize the absence of a relationship between cerebellar volume and executive dysfunction.

## Socioeconomic status and executive functions

Socioeconomic status (SES) also influences executive functions. Economic measures of SES include family income, income-to-needs ratio, and household wealth, among others. Social constructs that comprise SES include parental educational attainment, marital status, employment status, occupational prestige (Hollingshead, 1975). Studies of heathy controls have consistently found that children with higher SES have better executive functioning (Moffitt et al., 2011; Farah, 2017). A meta-analysis found that for studies with substantial variability in SES, the relationship between SES and executive functioning was small-to-medium in size (r = .22; Lawson, Hook, & Farah, 2018). Several theories regarding the causes of the relationship between SES and cognitive abilities (including executive functions) have been proposed (Bradley & Corwyn, 2002). Such theories include the abundance or dearth of cognitively stimulating materials, more nurturing parenting styles of high-SES caregivers, neurotoxic effects of chronic poverty-related stress, and negative attitudes of teachers toward students of low SES that result in less nurturing relationships between teachers and students. The question of which mechanisms affect executive functions in children with SBM and typically developing children will not be tested this study, but it is likely that all of them play some role in EFs.

Evidence exists that this relationship between SES and EFs is cross-cultural. In a study of Mexican and Colombian children aged 5-14, a hierarchical regression model—with age, type of school (public or private), and parental education as predictors and five performance measures of EFs as outcomes—was tested. After removing 38% of the variance attributable to age, parental education explained an additional 3-12% of variance in verbal EF scores depending on the measure. However, parental education explained a negligible amount of

variance for nonverbal EF tasks of cognitive flexibility and reasoning (Ardila, Rosselli, Matute, & Guajardo, 2005).

The impact of SES on EFs is important because EFs are often mediate the relationship between SES and various academic and functional outcomes, based on studies of typically developing children. Sektnan and colleagues found that the SES risk variables of minority status and maternal education were related to poorer reading, math, and vocabulary in first grade, but this relationship was partially mediated by behavioral regulation at 54 months and kindergarten (Sektnan, McClelland, Acock, & Morrison, 2010). Studies have found an EFs mediator of the relationship between SES and academic achievement in 54-66-month children (Dilworth-Bart, 2012; Fitzpatrick, McKinnon, Blair, & Willoughby, 2014).

## Socioeconomic status and executive functions in SBM

The relationship between socioeconomic status and executive functions is especially important to study in SBM. Children with SBM are more likely to live in economically disadvantaged communities than other children (Wasserman, Shaw, Selvin, Gould, & Syme, 1998). In fact, low maternal folic acid consumption, the strongest environmental predictor for SBM (Copp et al., 2015), is far more common in poor families than rich families (Wasserman et al., 1998).

The impact of SES on EFs in SBM can be conceptualized with Dennis's model of risk and reserve in childhood neural disorders (Dennis, 2000). According to the model, the following factors determine the presence or absence of cognitive impairment in the abnormal pediatric brain: age at injury, age at assessment, time since injury, biological risk factors, and environmental factors. Applying this model to neurobehavioral outcomes in SBM, age at

injury and time since injury are not relevant factors because they imply an acquired injury; SBM is not acquired in the way that, for example, TBI or brain tumors are acquired. Therefore, age, biological factors (e.g. primary and secondary neural insults of SBM), and environmental factors (e.g. SES) determine executive functioning in SBM.

Several studies have explicitly or implicitly applied this model to studying EFs in SBM. In a cluster analysis of neuropsychological functioning profiles (including executive functioning), SES (operationalized as parental education, employment, marital status, and occupation) differentiated the extremely low-to-borderline functioning cluster from the average functioning with verbal strength cluster, with a large effect size (d=1.12). However, it did not conclusively differentiate the low average-to-average functioning cluster from either of the other two clusters. Neurobiological risk factors of seizure history and lesion level did differentiate the three clusters, suggesting that socioeconomic risk may be a less sensitive predictor of EFs in SBM than neurobiological risk (Wasserman & Holmbeck, 2016). In a hierarchical model of informant-reported metacognitive dysfunction that included age as a predictor, adding neurobiological risk variables (number of shunt revisions and presence of seizures), explained an additional 23% of variance. In a similar model of behavioral regulation dysfunction, adding SES risk explained an additional 22% of variance. Interestingly, SES risk did not contribute significant unique variance to the model of metacognition and neurobiological risk did not contribute significant unique variance to the model of behavioral regulation (Brown et al., 2008).

## Socioeconomic status as a potential moderator of brain-EF relationships in SBM

Research into EFs of children with SBM have established neurobiological and socioeconomic risk factors as main effects. However, less research has been conducted that tests an interactive model of the two sets of factors. In other words, to what extent does the relationship between neurobiological risk and EF vary as a function of the SES gradient? Brown and colleagues found an interaction approaching significance ($p=.06$) of neurobiological risk and SES on metacognition but not behavioral regulation, with unreported effect sizes (Brown et al., 2008).

In typically developing children, family income moderated the relationship between global cortical thickness and performance on tasks of inhibition and cognitive flexibility. Children with thinner cortices performed well regardless of family income. But in children with thicker cortices, high family income protected against worse performance on tasks of inhibition and cognitive flexibility (Brito, Piccolo, & Noble, 2017). No study to date has examined the potential moderation of SES on the relationship between cerebellar structure and EFs in SBM.

## Aims

The current study aims to address the following questions:

1. How does regional cerebellar volume predict EFs? Does it differ (in magnitude or direction) in children with SBM compared to TD children?
2. In children with SBM, does the prediction of regional cerebellar volume on EFs depend on socioeconomic status of the child?

## Method

*Participants*

74 children and adolescents with SBM and 25 typically developing children and adolescents were recruited from a previous large-scale study that examined neurobehavioral outcomes of spina bifida (Fletcher et al., 2005). Participants with SBM were initially recruited from clinics at Shriners Hospital and Texas Children's Hospital in Houston, Texas, USA. Typically developing children were recruited from the community or from advertisements. The participants were a subset of a larger cohort of children and adults: 1 with spina bifida lipomeningocele, 2 with spina bifida lipomyelomeningocele, 5 with spina bifida meningocele, 516 with SBM, and 138 TD.

The SBM group had the following medical characteristics: 59 with lower-level lesions and 15 with upper-level lesions; 70 with Chiari II malformation, 2 with Chiari I malformation, and 2 without Chiari malformation; 54 without history of seizures, 6 with seizures in the past, 3 with current history of seizures, and 11 unreported; 23 with corpus callosum dysgenesis, 47 with corpus callosum hypoplasia, and 4 with a normal corpus callosum; 11 with no history of shunt revisions, 22 with one shunt revision, 24 with 2-4 shunt revisions, 7 with 5-9 shunt revisions, 2 with 10 or more shunt revisions, and 8 unreported; 49 without hydrocephalus at the time of assessment, 25 with hydrocephalus at assessment. Among those with reported hydrocephalus at assessment, 14 cases were mild, 9 were moderate, and 2 were severe. 6 SBM participants and 0 typically developing participants were excluded due to standard scores below 70 on both the Verbal Reasoning and Abstract/Visual Reasoning indices of the Stanford-Binet Intelligence Scale-Fourth Edition or

a score below 70 on one index and an unreported score on the other index (Thorndike, Hagen, & Sattler, 1986).

*Measures*

Socioeconomic status

Socioeconomic status was assessed using the Hollingshead four-factor index (Hollingshead, 1975). The four factors—marital status, retired/employed status, educational attainment, and occupational prestige—are collected from the parents and combined into one score that is a continuous variable. Notably, the Hollingshead index does not use family income as a factor.

Educational attainment is scored on a scale of 1-7 points: 1 = less than 7$^{th}$ grade, 2 = junior high school (9$^{th}$ grade), 3 = partial high school (10$^{th}$ or 11$^{th}$ grade), 4 = high school graduate, 5 = at least one year of college without graduating or specialized training, 6 = college or university graduate, 7 = graduate professional degree.

Occupational prestige is scored on a scale of 1-9: 1 = farm laborer/menial service worker, 2 = unskilled worker, 3 = machine operators and semiskilled workers, 4 = smaller business or farm owner (valued at less than $25,000), skilled manual worker, craftsman, or tenant farmer, 5 = clerical and sales worker, small farm and business owner (valued at $25,000-$50,000), 6 = technician, professional, small business owner (valued at $50,000-$75,000), 7 = small business or farm owner (valued at $75,000-$100,000), manager, or minor professional, 8 = medium-sized business or farm owner (valued at $100,000-$250,000), administrator, or lesser professional, 9 = owner of farm or business (valued at greater than $250,000), major professional, or higher executive. Occupations are categorized according to the United States

Census codes for occupations (for more detailed descriptions of each score and of which census codes correspond to which scores, refer to Hollingshead, 1975).

If two employed parents live in the household, educational attainment and occupational status are averaged between the two parents. If only one parent lives in the household, that parent's educational attainment and occupational status are scored. If the parent(s) is/are retired, the most recent occupation is used to score occupational status.

Occupation is scaled by a weight of 5 and education is scaled by a weight of 3. These are summed to create the total Hollingshead score. Therefore, the Hollingshead index scores can be expressed by the following formula:

$$SES = 5 * (occupation) + 3 * (education)$$

Executive functions

Executive functions were assessed using the Behavior Rating Inventory of Executive Function-Parent Report (from now on, simply termed BRIEF; Gioia et al., 2000). Unlike performance measures of EFs, the BRIEF is a parent-report questionnaire concerning the child's daily life, with an emphasis on EF issues that underlie dysfunctional behavior. These EFs more closely resemble complex EFs than the simple EFs of working memory, inhibition, and cognitive flexibility that were constructed through controlled laboratory experiments. Although Working Memory and Inhibit are scales of the BRIEF, the items that comprise those scales are less concerned with what can be gleaned from performance measures and more concerned with complex daily living problems. For example, "Has trouble finishing tasks (chores, homework)" is an item of the Working Memory scale and "Interrupts others" is an item of the Inhibit scale. Although sustained attention and working memory are often

conceptualized as different constructs, the items intended to represent those constructs loaded onto the same factor and thus, were placed into one scale.

Items on are the BRIEF are scored as 1 = Never, 2 = Sometimes, 3 = Often. Each item on the BRIEF belongs to one of eight scales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. Inhibit, Shift, and Emotional Control are combined into the Behavioral Regulation Index and Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor are combined into the Metacognition Index. Scores for each item of a scale are summed to create the raw score and the raw scores of the scales are summed to create the index scores. There are also two validity scales: Negativity, which measures the extent to which the parent answers excessively negatively about her child and Inconsistency, which measures the extent to which the parent answers similar items in an inconsistent manner. The Inconsistency scale score is classified as Acceptable, Questionable, or Inconsistent. The Negativity scale score is classified as Acceptable, Elevated, or Highly elevated. No responses to the BRIEF fell into the Inconsistent range for the Inconsistency scale or the Highly elevated range for the Negativity scale. The scales and indices of the BRIEF have good-to-excellent internal consistency in clinical and normative samples ($0.80 < \alpha < .98$) and strong test-retest reliability in clinical and normative samples (.72-.92).

*MRI Analysis*

Image Acquisition

Participants who received an MRI were scanned in a research-exclusive Philips 3T MRI scanner with SENSE (Sensitivity Encoding) technology and an 8-channel phased array head

coil at the McGovern Medical School at The University of Texas Health Science Center in Houston, Texas, USA. Following a scout sequence, T1-weighted images were acquired in the sagittal plane with the following parameters: slice thickness = 1.5 mm, voxel size = .94 mm x .94 mm x 1.5 mm, TR = 6.50–6.70 ms, TE = 3.04–3.14 ms, flip angle = 8°, FOV = 240 x 240 $mm^2$, matrix = 256 x 256 $mm^2$.

Brain Segmentation and Parcellation

Although automated segmentation/parcellation programs like FreeSurfer are popular in volumetric research, they are not the best option for our cerebellar analyses. Most programs do not parcellate the cerebellum with much specificity (for example, FreeSurfer only parcellates the cerebellum into left and right cortex and white matter). Programs that do parcellate the cerebellum with good specificity often rely on a template of a typically developing brain in order to register participants' brains. However, abnormal cerebellar structure, caused by the Chiari II malformation is characteristic of SBM. Therefore, manual tracing of the cerebellum was the best method. The cerebellum was parcellated while viewing the T1 weighted slices via manual tracing by one experienced rater with extensive knowledge of cerebellar anatomy (JJ), using previously-established protocols (Juranek et al., 2010; Pierson, Corson, Sears, Alicata, Magnotta et al., 2002). Four cerebellar regions were traced: 1) corpus medullare, (central white matter and output nuclei), 2) anterior lobe (lobules I–V, bounded by the most posterior point of the fourth ventricle, corpus medullare, and primary fissure), 3) superior-posterior lobe (lobe VI and crus I of VIIA, bounded by the primary fissure, corpus medullare, and horizontal fissure), and 4) inferior–posterior lobe (crus II of VIIA, VIIB, VIII, IX, and X, bounded by the most posterior point of the fourth

ventricle, corpus medullare, and horizontal fissure). To simplify our model, the inferior-posterior and super-posterior lobes were combined into a posterior lobe composite. Notably, the posterior lobe contains regions that underlie executive functions (crus I and II) as well as regions that underlie sensorimotor functions (lobes VI and VIII). The corpus medullare contains the white matter pathways that connect crus I and II to other regions of the central executive network.

## Hypotheses

The number associated with each hypothesis corresponds to the same number in the "Aims" section.

1. In our analysis of how cerebellar volume predicts EFs and whether it differs between groups:
    a. Test of simple effects
        i. Volume of the posterior cerebellum will significantly predict raw scores on both the metacognition and behavioral regulation indices of the BRIEF, such that greater volume indicates less executive dysfunction.
        ii. Volume of the corpus medullare will significantly predict raw scores on both the metacognition and behavioral regulation indices of the BRIEF, such that greater volume indicates less executive dysfunction.
        iii. Volume of the anterior cerebellum will not significantly predict raw scores on either index of the BRIEF.
    b. Test of group x cerebellar volume interactions

i. Group and volume of the posterior cerebellum will interact such that volume will predict EFs better for the SBM group than the TD group.
    1. Not enough research has been conducted to hypothesize whether this interaction will be stronger for the metacognition or behavioral regulation index. We will test this question as an exploratory analysis.

ii. Group and volume of the corpus medullare will interact such that volume will predict EFs better for the SBM group than the TD group.
    1. Not enough research has been conducted to hypothesize whether this interaction will be stronger for the metacognition or behavioral regulation index. We will test this question as an exploratory analysis.

iii. Group and volume of the anterior cerebellum will not interact to predict scores on either index of the BRIEF.

2. These analyses will focus on the subset of children diagnosed with SBM. We will be testing whether cerebellar volume predicts EFs differently depending on SES, assessed via the Hollingshead index. We expect to find the following:
    a. SES will interact with posterior cerebellar volume such that volume will predict EFs better as SES scores decrease.
        i. Not enough research has been conducted to hypothesize whether this interaction will be stronger for the metacognition or behavioral regulation index. We will test this question as an exploratory analysis.

b. SES will interact with the corpus medullare such that volume will predict EFs better as SES scores decrease.
    i. Not enough research has been conducted to hypothesize whether this interaction will be stronger for the metacognition or behavioral regulation index. We will test this question as an exploratory analysis.
c. SES will not interact with anterior cerebellum volume to predict scores on either index of the BRIEF.

## Statistical Methods

All analyses were conducted using R version 3.5.3 (R Core Team, 2019). Before conducting regression analyses, all variables in the models were standardized to simplify interpretation of regression coefficients. Hypothesis 1 was tested using a multivariate multiple regression model. Raw scores of the Behavioral Regulation and Metacognition indices were the dependent variables; group (TD vs. SBM), age, cerebellar volume for each region (anterior lobe, posterior lobe, corpus medullare), and the interaction between group and volume for each region were the independent variables. A full model was tested for which we examined which independent variables significantly predicted the multivariate, linear combination of the dependent variables. Next, we calculated the standardized regression weights for the independent variables on each dependent variable, the associated 95% confidence interval, the p-value, and the unique $R^2$ contributed to each dependent variable. These findings are identical to what we would find if we calculated two separate univariate multiple regressions: one with Behavioral Regulation as the dependent variable and one with Metacognition as the dependent variable.

Hypothesis 2 was tested using a multivariate multiple regression model. As in hypothesis 1, the dependent variables were the raw scores Behavioral Regulation and Metacognition indices. Because we are only testing children with SBM for this hypothesis, group was not in the model. The independent variables were SES score (as measured by the Hollingshead Index), age, cerebellar volume for each region (posterior lobe, anterior lobe, corpus medullare), and the interaction between SES score and volume for each region. A full model was tested for which we examined which independent variables significantly predicted the multivariate, linear combination of the dependent variables. After that, we calculated the standardized regression weights for the independent variables on each dependent variable, the associated 95% confidence interval, the p-value, and the unique $R^2$ contributed to each dependent variable.

Diagnostics were run on the regression models to test for multivariate normality of residuals and homoscedasticity of residuals. Multivariate normality of residuals was tested using the Henze-Zirkler method (Henze & Zirkler, 1990; Mecklin & Mundfrom, 2005). We also followed up with the Mardia test (Mardia, 1974) of multivariate skewness and kurtosis, and used a multivariate Q-Q plot (Korkmaz, Goksuluk, & Zararsiz, 2014) to detect outliers. We did not remove any outliers from the analyses. Tests of homoscedasticity for a multivariate multiple regression are not common are not available in any R package. Instead we tested homoscedasticity of residuals for each univariate regression model separately using the Breusch-Pagan method (Breusch & Pagan, 1979).

## Results

**Aim 1: What is the relationship between regional cerebellar volume and EFs? Does that relationship differ in children with SBM compared to TD children?**

Full model:

Using Pillai's Trace, we tested which predictor variables were significantly related to the multivariate, linear combination of raw scores of the BRIEF Metacognition and Behavioral Regulation indices. Results are reported in Table 1. Group (trace = .122, approximate F(2, 89) = 6.17, p = .003) and age (trace = .114, approximate F(2, 89) = 5.72, p = .004) jointly predicted the BRIEF scores while the other predictors did not.

Table 1: Test of the full Multivariate model, including joint prediction of BRIEF Behavioral Regulation and Metacognition index.

| Independent Variable | Pillai's trace | Approximate F | p |
|---|---|---|---|
| Group | .122 | 6.17 | .003 |
| Age | .114 | 5.72 | .005 |
| Anterior Cerebellum Volume | .018 | .793 | .46 |
| Posterior Cerebellum Volume | .021 | .934 | .40 |
| Corpus Medullare Volume | .004 | .179 | .84 |
| Group x Anterior Cerebellum Volume | .024 | 1.11 | .33 |
| Group x Posterior Cerebellum Volume | .031 | 1.44 | .24 |
| Group x Corpus Medullare Volume | .024 | 1.08 | .34 |

Behavioral Regulation:

Next, we examined association with each of the dependent variables entered in the multivariate model. The model was significant for the dependent variable Behavioral Regulation: ($F(8, 90)=3.71$, $p<.001$), with a multiple $R^2 = .248$ and an adjusted $R^2 = .181$. On tests of regression coefficients, age explained 7.6% of the variance and was a significant

predictor (β = -.308, 95% CI = [-.51, -.10]); older age was associated with better behavioral regulation. Group significantly predicted behavioral regulation at a trend level (β = .915, 95% CI = [-.07, 1.89], p = .07), $R^2$ = .10. No other independent variables significantly predicted behavioral regulation. Detailed results can be found in Table 2.

Metacognition:

The model was also significant for the dependent variable Metacognition (F(8,90) = 5.63, p<.0001), with a multiple $R^2$ = .333 and an adjusted $R^2$ = .274. On tests of regression coefficients, group was a significant predictor of Metacognition (β = 1.33, 95% CI = [.40, 2.25], p = .005), $R^2$ = 17.1%. The SBM group had worse metacognitive functioning than the TD group. No other independent variables significantly predicted Metacognition. Detailed results can be found on Table 2.

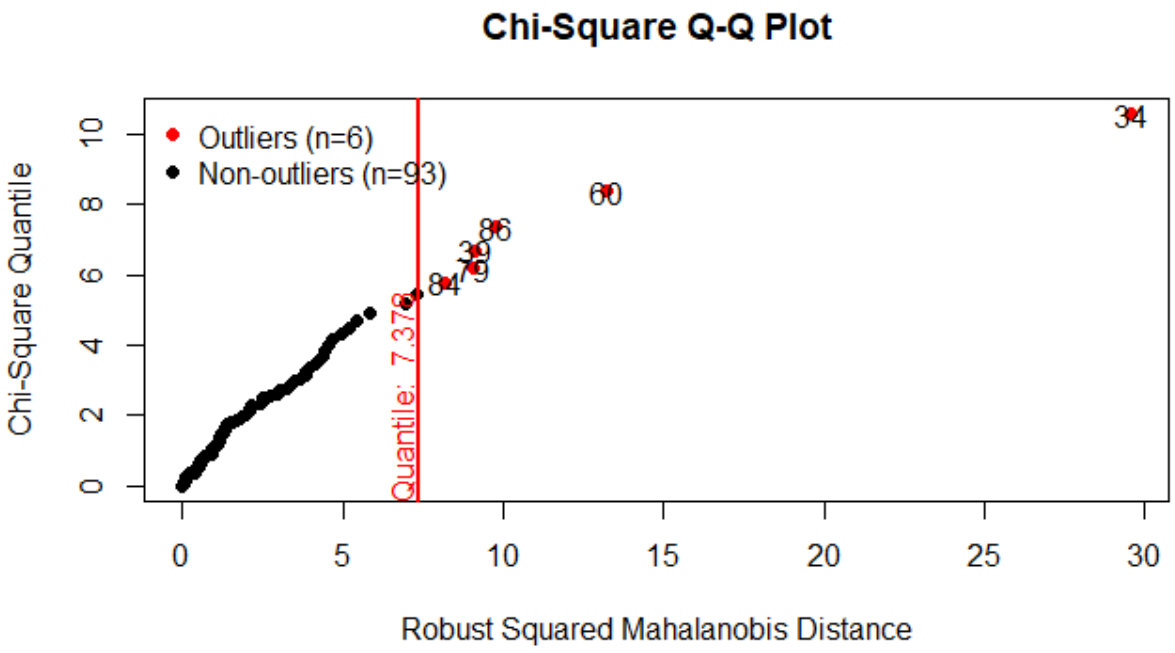
Table 2: Multivariate multiple regression model with regression weights, 95% confidence intervals, p values, and relative importance (i.e., $R^2$) of the predictors.

| | Behavioral Regulation | | | | Metacognition | | | |
|---|---|---|---|---|---|---|---|---|
| **Independent Variable** | **β** | **95% CI** | **p** | **$R^2$** | **β** | **95% CI** | **p** | **$R^2$** |
| Intercept | -0.7 | [-1.66, .25] | .15 | N/A | -1.11 | [-2.01, -.21] | .02 | N/A |
| Group | 0.915 | [-.07, 1.89] | .07 | .103 | 1.33 | [.40, 2.25] | .005 | .171 |
| Age | -0.308 | [-.51, -.10] | .004 | .076 | -0.103 | [-.29, .09] | .29 | .01 |
| Anterior Cerebellum Volume | 0.024 | [-.67, .72] | .94 | .021 | -0.243 | [-.90, .41] | .46 | .039 |
| Posterior Cerebellum Volume | -0.151 | [-.99, .69] | .72 | .023 | 0.112 | [-.68, .90] | .78 | .066 |
| Corpus Medullare Volume | 0.213 | [-.41, .84] | .50 | .02 | -0.017 | [-.61, .57] | .95 | .032 |
| Group x Anterior Cerebellum Volume | 0.073 | [-.66, .80] | .84 | .0015 | 0.402 | [-.68, .90] | .25 | .009 |
| Group x Posterior Cerebellum Volume | 0.149 | [-.79, 1.09] | .75 | .001 | -0.41 | [-1.30, .47] | .36 | .005 |
| Group x Corpus Medullare Volume | -0.212 | [-.96, .54] | .58 | .0025 | 0.19 | [-.52, .90] | .59 | .001 |

Regression Diagnostics:

The Henze-Zirkler test indicated that the residuals trended toward violating the assumption of multivariate normality (Test statistic = 0.889, p = .08). The Mardia tests found that the residuals were significantly skewed (Test statistic = 19.28, p < .001) but not significantly leptokurtic or platykurtic (Test statistic = 1.40, p = .16). Fig 1. shows a Q-Q plot of multivariate outliers. The Breusch-Pagan test found that assumption of homoscedasticity of residuals was not violated for Behavioral Regulation (Test statistic = 12.64, p = .12) or Metacognition (Test statistic = 10.07, p = .26).

Figure 1: Q-Q plot of multivariate outliers for Aim 1




To examine possible multicollinearity, we performed a correlation between volumes of the three cerebellar regions. Posterior cerebellum/corpus medullare were highly correlated (r =

.822, p < .001), while posterior cerebellum/anterior cerebellum (r = -.177, p = .08) and anterior cerebellum/corpus medullare (r = -.105, p = .30) were not significantly correlated.

**Aim 2: Does the relationship between cerebellar volume and EFs in children with SBM differ depending on socioeconomic status of the child?**

Full model:

Using Pillai's Trace, we tested which independent variables were significantly predicted the multivariate, linear combination of raw scores of the BRIEF Metacognition and Behavioral regulation indices. Age (trace = .107, approximate F(2, 64) = 3.84, p = .03) jointly predicted the BRIEF scores while the other predictors did not. Detailed results are reported in Table 3.

Table 3: Test of joint prediction of Behavioral Regulation and Metacognition indices (SBM group only)

| Independent Variable | Pillai's trace | Approximate F | p |
|---|---|---|---|
| SES | .058 | 1.96 | .15 |
| Age | .107 | 3.84 | .03 |
| Anterior Cerebellum Volume | .025 | 1.57 | .44 |
| Posterior Cerebellum Volume | .047 | 0.83 | .22 |
| Corpus Medullare Volume | .012 | 0.39 | .68 |
| SES x Anterior Cerebellum Volume | .037 | 1.22 | .30 |
| SES x Posterior Cerebellum Volume | .012 | 0.40 | .67 |
| SES x Corpus Medullare Volume | .002 | 0.05 | .95 |

Behavioral Regulation:

The model was significant at the trend level for the dependent variable Behavioral Regulation (F(8, 65) = 2.01, p = .059). On tests of regression coefficients, age significantly predicted (β = -.29, p = .03). The model had a multiple $R^2$ = .20 and adjusted $R^2$ = .10.

Furthermore, age explained more variance than any other predictor (9.9%). SES and the cerebellum volume measurements as simple effects explained little variance but their interactions with SES explained more variance. SES x anterior cerebellum volume explained 2% of variance, SES x posterior cerebellum volume explained 2.8% of variance, and SES x corpus medullare volume explained 2.7% of variance. Detailed results can be found on Table 4.

Metacognition:

The model was not significant for the variable Metacognition ($F(8, 65) = 1.59$, $p = .15$), multiple $R^2 = .16$, adjusted $R^2 = .06$. Nonetheless, we decided to examine the model and report effect sizes and confidence intervals. Detailed results can be found on Table 4.

Table 4: Multivariate multiple regression model with regression weights, 95% confidence intervals, p values, and relative importance (i.e., $R^2$) of the predictors (SBM group only).

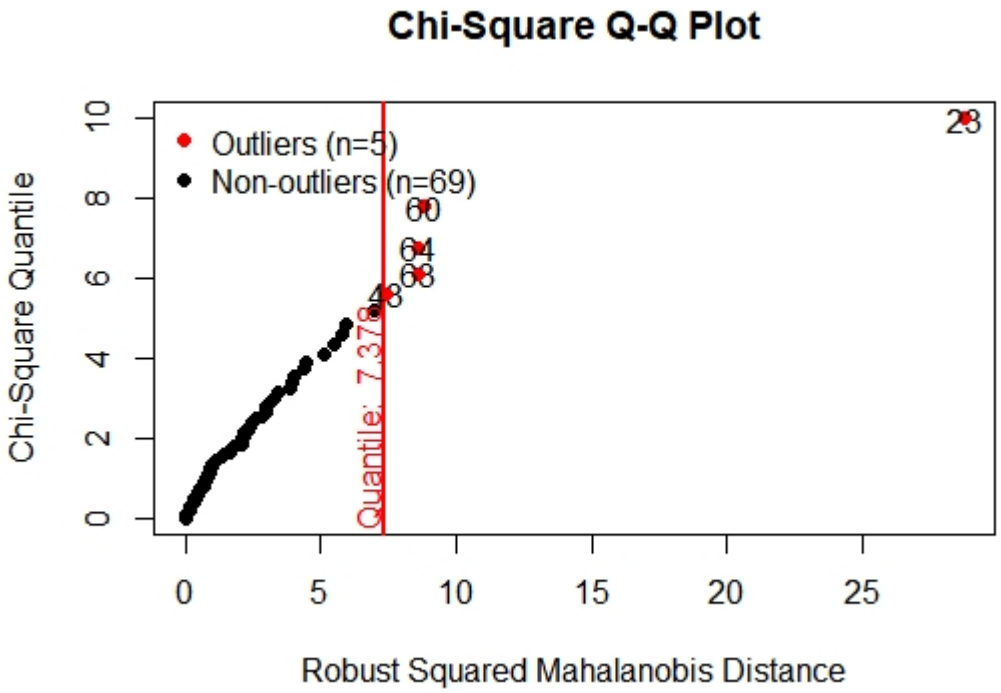
| | Behavioral Regulation | | | | Metacognition | | | |
|---|---|---|---|---|---|---|---|---|
| **Independent Variable** | **β** | **95% CI** | **p** | **$R^2$** | **β** | **95% CI** | **p** | **$R^2$** |
| Intercept | 0.237 | [-.04, .52] | 0.10 | N/A | 0.222 | [-.04, .48] | 0.09 | N/A |
| SES | -0.073 | [-.35, .20] | 0.59 | .004 | 0.086 | [-.17, .34] | 0.50 | .050 |
| Age | -0.29 | [-.55, -.03] | 0.03 | .099 | -0.062 | [-.30, .18] | 0.60 | .012 |
| Anterior Cerebellum Volume | -0.022 | [-.13, .37] | 0.35 | .016 | 0.149 | [-.08, .38] | 0.21 | .034 |
| Posterior Cerebellum Volume | 0.015 | [-.50, .53] | 0.95 | .002 | -0.287 | [-.77, .19] | 0.24 | .022 |
| Corpus Medullare Volume | -0.022 | [-.55, .50] | 0.93 | .003 | 0.137 | [-.35, .62] | 0.57 | .006 |
| SES x Anterior Cerebellum Volume | -0.16 | [-.43, .11] | 0.24 | .02 | -0.021 | [-.27, .23] | 0.87 | .0003 |
| SES x Posterior Cerebellum Volume | -0.21 | [-.76, .35] | 0.45 | .028 | -0.227 | [-.74, .28] | 0.38 | .024 |
| SES x Corpus Medullare Volume | -0.043 | [-.55, .46] | 0.87 | .027 | 0.014 | [-.45, .48] | 0.95 | .014 |

Regression Diagnostics

The Henze-Zirkler test found that the residuals did not significantly deviate from multivariate normality (Test statistic = .784, p = .12). However, the Mardia test found that

the residuals were significantly skewed (Test statistic = 15.43, p = .004). Fig. 2 shows a Q-Q plot of multivariate outliers. The Breusch-Pagan test did not find significant heteroscedasticity for the models of Behavioral Regulation (Test statistic = 7.70, p = .46) or Metacognition (Test statistic = 6.03, p = .64).

Figure 2: Q-Q plot of multivariate outliers for Aim 2




## Discussion

This study investigated the associated between morphometry of the cerebellum and executive functioning in children with spina bifida myelomeningocele (Aim 1), and the potential moderating factor of socioeconomic status on that relationship (Aim 2). With respect to Aim 1, we hypothesized that two specific regions of the cerebellum (posterior and corpus medullare), shown to contribute to EFs in typically developing populations, would

predict EFs in our sample of TD children and children with SBM. We also hypothesized that the association between these cerebellar regions and EFs would be stronger in children with SBM. However, these hypotheses were not supported by the data. Consistent with prior results (Burmeister, Hannay, Copeland, Fletcher, Boudousquie, & Dennis, 2005), model results revealed that EFs were significantly associated with group (TD vs. SBM) and age. Specifically, group predicted metacognition and predicted behavioral regulation at the trend level, with the SBM group evidencing worse functioning in those domains. Moreover, older age was associated with better executive functioning, specifically better behavioral regulation.

With respect to Aim 2, we hypothesized that SES would moderate the relationship between posterior cerebellum volume and executive functioning in children with SBM. We also hypothesized that SES would moderate the relationship between corpus medullare volume and executive functioning in children with SBM. However, these hypotheses were not supported by the data. The only independent variable that significantly predicted EFs in children with SBM was age, and this predictor was only significant for behavioral regulation.

That age explains so much variance in the Behavioral Regulation index suggests that children develop more effective behavioral regulation skills as they age. This is also true for the SBM group. When examining cognition in children with spina bifida, we want to know whether development in a given domain is delayed and whether that development plateaus during childhood or continues into adulthood. These results suggest that development of behavioral regulation continues into adulthood; however, these children remain delayed upon entering adulthood. However, age was not a significant predictor of scores on the Metacognition index, when examining the whole sample and when examining the SBM

group only (Table 4). This suggests the relationship between aging and improving metacognition is not as strong as the relationship between aging and improving behavioral regulation in children with SBM.

Despite our hypotheses, we found no significant associations between cerebellar structure and executive functioning. Several factors could account for the lack of support for our hypotheses. One factor concerns how we obtained our measure regional cerebellar volume. This study utilized manual tracing by an experienced rater with extensive knowledge of the heterogeneous cerebellar morphology in SBM. Despite the qualifications of the rater, manual tracing remains inherently susceptible to human error. When the paper reporting these cerebellar regional volume measurements was published (Juranek et al., 2010), this was the optimal method given the technology available then. However, newer neuroimaging software may have segmented the cerebellum more accurately than even an experienced human rater.

Our findings could potentially be explained by our choice of imaging modality: structural MRI. Neuroimaging researchers examine volume at the macro level because it can represent microstructural properties of brain regions. For example, a larger posterior cerebellum could represent more gray matter (dendrites, cell bodies) while a larger corpus medullare (i.e. central white matter) could represent greater myelination, the latter potentially indicating more connections to the executive control network and increased efficiency of those connections. However, this assumption does not always hold, and other imaging modalities may be better suited to measure function in the cerebellum. Indeed, the neuroimaging studies that provided the most compelling evidence for the role of the cerebellum (specifically, the posterior lobe) in EFs employed different imaging modalities and analytical methods from this study: resting-state functional connectivity fMRI, task-based fMRI, and diffusion tensor

imaging (Habas et al., 2009; Salmi et al., 2010). fMRI uses cerebral blood flow to infer function and that could be more sensitive to individual variation in executive functioning. DTI uses diffusion of water molecules in white matter tissue to infer the structural integrity of white matter tracts; this could be a more accurate measure of efficiency of connections between the cerebellum and other regions of the central executive network than volume of the corpus medullare.

Measuring volume of three cerebellar regions exclusively may represent a suboptimal strategy for examining the brain and executive functioning. EFs are high-level functions whose processes are widely distributed across several neural networks. Neuroimaging techniques that examine associations between the cerebellum and other neural networks that comprise EFs could measure the cerebellum's role in EFs better than the current study. For example, a functional connectivity fMRI study could measure the connectedness of the cerebellum with other regions of the central executive network and test the association between that connectedness and EFs.

Our findings could also be explained by our tool used to measure EFs: the BRIEF. Unlike most EF measures, the BRIEF is an informant-report questionnaire, not a performance-based measure. Tabletop and computerized (Bauer, Hanson, Pierson, Davison, & Pollak, 2009) tests of executive functioning may be more sensitive to variation in cerebellar subregion volume than informant-reported measures of executive functioning. Additionally, the measure we chose to assess SES could have impacted our results. The Hollingshead index measures occupational prestige and educational attainment. Although these factors are certainly important, it may not capture all the socioeconomic struggles of families with SBM. Children with SBM tend to live in lower income families than TD children, and their daily-

living needs requires many more resources than TD children. A measure of adequacy of resources (Dunst & Leet, 1987) or income may be related to EFs in a different way from a measure of occupational prestige and educational attainment.

Another potential explanation for our null findings is the methodological limitations of our study. Our variables had poor precision of measurement, partly because of the cognitive and neural heterogeneity in SBM. Furthermore, Even when estimated regression weights were large (e.g., in $\beta = -.41$ for interaction of group and posterior lobe volume on Metacognition index scores), the 95% confidence intervals were very wide (e.g., in this case, [-1.30, .47]). Our model also likely suffered from low statistical power. According to our a priori multivariate power analyses, with the estimated sample size (99), number of dependent variables (2), and number of independent variables (5: 3 cerebellum regions, two covariates), and alpha of .05, we had sufficient power (.80) to detect a medium effect size (r squared = .08, power = .80), and large effect size (r squared = .25, power = .99) but not a small effect size (r squared = .05, power = .56). Indeed, we found that for Aim 1, our model explained 18% of variance in behavioral regulation scores and 27% of variance in metacognition scores, but only group and age emerged as significant predictors. However, these power analyses refer to finding statistical significance for the full model. The effect size for necessary to reach statistical significance for individual independent variables is probably much larger. In addition, because of the diffuse neural insults in spina bifida, the cerebellum likely explains, at most, a small proportion of variance in executive functioning. Hydrocephalus, shunting, lesion level, and history of seizures are all correlates of poorer neurocognitive outcome in spina bifida (Wasserman et al., 2016), and other neural insults of spina bifida like corpus callosum malformation and excess gyrification in the frontal lobes

may explain variance in executive functioning as well. Furthermore, children with spina bifida have functional impairments that typically developing children do not. Most children with spina bifida struggle with walking or do not walk. Many do not have urinary or bowel control and they must follow a bowel regimen that typically developing children do not. These functional challenges affect and are affected by the development of executive functions in children with SBM (O'Hara & Holmbeck, 2013). In response to such functional challenges, psychosocial factors like resilience may play a larger role in development of EFs in children with SBM than TD children. Ultimately, there are many neuroanatomical and psychosocial factors that especially affect children with SBM and their ability to develop cognitive functioning, including EFs. The cerebellum, if it has a role, likely plays a small role and is just one piece of the complex picture of spina bifida myelomeningocele in children.

## References


Ardila, A., Rosselli, M., Matute, E., & Guajardo, S. (2005). The influence of the parents' educational level on the development of executive functions. *Developmental neuropsychology, 28*(1), 539–560.

Baddeley, A. D., & Hitch, G. J. (1994). Developments in the Concept of Working Memory. *Neuropsychology, 8*(4), 485–493.

Bassuk, A. G., & Kibar, Z. (2009). Genetic basis of neural tube defects. *Seminars in pediatric neurology, 16*(3), 101–110.

Bauer, P. M., Hanson, J. L., Pierson, R. K., Davidson, R. J., & Pollak, S. D. (2009). Cerebellar volume and cognitive functioning in children who experienced early deprivation. *Biological psychiatry, 66*(12), 1100–1106.

Blair, C., & Razza, R. P. (2007). Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in kindergarten. *Child development, 78*(2), 647–663.

Boone, D., Parsons, D., Lachmann, S. M., & Sherwood, T. (1985). Spina bifida occulta: lesion or anomaly? *Clinical radiology, 36*(2), 159–161.

Bostan, A. C., Dum, R. P., & Strick, P. L. (2013). Cerebellar networks with the cerebral cortex and basal ganglia. *Trends in cognitive sciences, 17*(5), 241–254.

Bradley, K. A., Juranek, J., Romanowska-Pawliczek, A., Hannay, H. J., Cirino, P. T., Dennis, M., et al. (2016). Plasticity of Interhemispheric Temporal Lobe White Matter Pathways Due to Early Disruption of Corpus Callosum Development in Spina Bifida. *Brain connectivity, 6*(3), 238–248.

Breusch, T. S., & Pagan, A. R. (1979). A Simple Test for Heteroscedasticity and Random Coefficient Variation. *Econometrica, 47*(5), 1287–1294.

Brito, N. H., Piccolo, L. R., & Noble, K. G. (2017). Associations between cortical thickness and neurocognitive skills during childhood vary by family socioeconomic factors. *Brain and cognition, 116*, 54–62.

Brocklehurst, G. (1969). A quantitative study of a spina bifida foetus. *The Journal of pathology, 99*(3), 205–211.

Burmeister, R., Hannay, H. J., Copeland, K., Fletcher, J. M., Boudousquie, A., & Dennis, M. (2005). Attention problems and executive functions in children with spina bifida and hydrocephalus. *Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence, 11*(3), 265–283.

Dattalo, P. (2013). *Analysis of multiple dependent variables. Pocket guides to social work research methods.* New York: Oxford University Press.

Dennis, M., & Barnes, M. A. (2010). The cognitive phenotype of spina bifida meningomyelocele. *Developmental disabilities research reviews, 16*(1), 31–39.

Dennis, M., Edelstein, K., Hetherington, R., Copeland, K., Frederick, J., Blaser, S. E., et al. (2004). Neurobiology of perceptual and motor timing in children with spina bifida in relation to cerebellar volume. *Brain : a journal of neurology, 127*(Pt 6), 1292–1301.

Dennis, M., Jewell, D., Hetherington, R., Burton, C., Brandt, M. E., Blaser, S. E., & Fletcher, J. M. (2008). Verb generation in children with spina bifida. *Journal of the International Neuropsychological Society : JINS, 14*(2), 181–191.

Dennis, M., Landry, S. H., Barnes, M., & Fletcher, J. M. (2006). A model of neurocognitive function in spina bifida over the life span. *Journal of the International Neuropsychological Society : JINS*, *12*(2), 285–296.

Dennis, M., Simic, N., Bigler, E. D., Abildskov, T., Agostino, A., Taylor, H. G., et al. (2013). Cognitive, affective, and conative theory of mind (ToM) in children with traumatic brain injury. *Developmental cognitive neuroscience*, *5*, 25–39.

Diamond, A. (2013). Executive functions. *Annual review of psychology*, *64*, 135–168.

Dilworth-Bart, J. E. (2012). Does executive function mediate SES and home quality associations with academic readiness? *Early Childhood Research Quarterly*, *27*(3), 416–425.

Disatnik, D., Sivan, L. (2016). The multicollinearity illusion in moderated regression analysis. *Marketing Letters*, *27*(2), 403–408.

Dunst, C. J., & Leet, H. E. (1987). Measuring the adequacy of resources in households with young children. *Child: care, health and development*, *13*(2), 111–125.

Fitzpatrick, C., McKinnon, R.D., Blair, C.B., Willoughby, M.T. (2014). Do preschool executive function skills explain the school readiness gap between advantaged and disadvantaged children? *Learning and instruction*, *30*, 25–31.

Fletcher, J. M., Brookshire, B. L., Landry, S. H., Bohan, T. P., Davidson, K. C., Francis, D. J., et al. (1996). Attentional skills and executive functions in children with early hydrocephalus. *Developmental neuropsychology*, *12*(1), 53–76.

Fletcher, J. M., Copeland, K., Frederick, J. A., Blaser, S. E., Kramer, L. A., Northrup, H., et al. (2005). Spinal lesion level in spina bifida: a source of neural and cognitive heterogeneity. *Journal of neurosurgery*, *102*(3 Suppl), 268–279.

Gioia, G. A. (2000). *BRIEF: Behavior rating inventory of executive function professional manual*. Odessa FL: Psychological Assessment Resources.

Globas, C., Bösch, S., Zühlke, C., Daum, I., Dichgans, J., & Bürk, K. (2003). The cerebellum and cognition. Intellectual function in spinocerebellar ataxia type 6 (SCA6). *Journal of neurology, 250*(12), 1482–1487.

Goldwasser, M. A., & Fitzmaurice, G. M. (2001). Multivariate linear regression analysis of childhood psychopathology using multiple informant data. *International Journal of Methods in Psychiatric Research, 10*(1), 1–10.

Gottwald, B., Wilde, B., Mihajlovic, Z., & Mehdorn, H. M. (2004). Evidence for distinct cognitive deficits after focal cerebellar lesions. *Journal of neurology, neurosurgery, and psychiatry, 75*(11), 1524–1531.

Gottwald, B., Mihajlovic, Z., Wilde, B., & Mehdorn, H. M. (2003). Does the cerebellum contribute to specific aspects of attention? *Neuropsychologia, 41*(11), 1452–1460.

Grafman, J., Litvan, I., Massaquoi, S., Stewart, M., Sirigu, A., & Hallett, M. (1992). Cognitive planning deficit in patients with cerebellar atrophy. *Neurology, 42*(8), 1493–1496.

Granero, R., Louwaars, L., & Ezpeleta, L. (2015). Socioeconomic status and oppositional defiant disorder in preschoolers: parenting practices and executive functioning as mediating variables. *Frontiers in psychology, 6*, 1412.

Greene, N. D. E., & Copp, A. J. (2014). Neural tube defects. *Annual review of neuroscience, 37*, 221–242.

Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C. F., Menon, V., & Greicius, M. D. (2009). Distinct cerebellar contributions to intrinsic connectivity networks. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 29*(26), 8586–8594.

Hannay, H. J. (2000). Functioning of the corpus callosum in children with early hydrocephalus. *Journal of the International Neuropsychological Society : JINS, 6*(3), 351–361.

Hannay, H. J., Dennis, M., Kramer, L., Blaser, S., & Fletcher, J. M. (2009). Partial agenesis of the corpus callosum in spina bifida meningomyelocele and potential compensatory mechanisms. *Journal of clinical and experimental neuropsychology, 31*(2), 180–194.

Heffelfinger, A. K., Koop, J. I., Fastenau, P. S., Brei, T. J., Conant, L., Katzenstein, J., et al. (2008). The relationship of neuropsychological functioning to adaptation outcome in adolescents with spina bifida. *Journal of the International Neuropsychological Society : JINS, 14*(5), 793–804.

Henze, N., & Zirkler, B. (1990). A class of invariant consistent tests for multivariate normality. *Communications in Statistics - Theory and Methods, 19*(10), 3595–3617.

Hollingshead, A. (1975). *Four factor index of social status*. New Haven, CT: Yale University, Department of Sociology.

Hubert, B., Guimard, P., Florin, A., & Tracy, A. (2015). Indirect and Direct Relationships Between Self-Regulation and Academic Achievement During the Nursery/Elementary School Transition of French Students. *Early Education and Development, 26*(5-6), 685–707.

Huberty, C. J., & Morris, J. D. (1989). Multivariate analysis versus multiple univariate analyses. *Psychological Bulletin, 105*(2), 302–308.

Işik, U. (2008). Seizures in Children with Myelomeningocele. In *The Spina Bifida* (pp. 297–301). Milano: Springer Milan.

Jacobson, L. A., Tarazi, R. A., McCurdy, M. D., Schultz, S., Levey, E., Mahone, E. M., & Zabel, T. A. (2013). The Kennedy Krieger Independence Scales-Spina Bifida Version: a measure of executive components of self-management. *Rehabilitation psychology, 58*(1), 98–105.

Juranek, J., Dennis, M., Cirino, P. T., El-Messidi, L., & Fletcher, J. M. (2010). The cerebellum in children with spina bifida and Chiari II malformation: Quantitative volumetrics by region. *Cerebellum (London, England), 9*(2), 240–248.

Juranek, J., Fletcher, J. M., Hasan, K. M., Breier, J. I., Cirino, P. T., Pazo-Alvarez, P., et al. (2008). Neocortical reorganization in spina bifida. *NeuroImage, 40*(4), 1516–1522.

Juranek, J., & Salman, M. S. (2010). Anomalous development of brain structure and function in spina bifida myelomeningocele. *Developmental disabilities research reviews, 16*(1), 23–30.

Kalnins, A. (2018). Multicollinearity: How common factors cause Type 1 errors in multivariate regression. *Strategic Management Journal, 39*(8), 2362–2385.

Karatekin, C., Lazareff, J. A., & Asarnow, R. F. (2000). Relevance of the cerebellar hemispheres for executive functions. *Pediatric Neurology, 22*(2), 106–112.

Kelly, N. C., Ammerman, R. T., Rausch, J. R., Ris, M. D., Yeates, K. O., Oppenheimer, S. G., & Enrile, B. G. (2012). Executive functioning and psychological adjustment in children and youth with spina bifida. *Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence, 18*(5), 417–431.

Korkmaz, S., & Dincer, G., Zararsiz, G. (2014). MVN: An R Package for Assessing Multivariate Normality. *The R Journal, 6*(2), 151–162.

Landry, S. H., Taylor, H. B., Swank, P. R., Barnes, M., & Juranek, J. (2013). Longitudinal mediators of social problem solving in spina bifida and typical development. *Rehabilitation psychology, 58*(2), 196–205.

Lawson, G. M., Hook, C. J., & Farah, M. J. (2018). A meta-analysis of the relationship between socioeconomic status and executive function performance among children. *Developmental science, 21*(2).

Lehto, J. E., Juujärvi, P., Kooistra, L., & Pulkkinen, L. (2003). Dimensions of executive functioning: Evidence from children. *British Journal of Developmental Psychology, 21*(1), 59–80.

Lennon, J. M., Klages, K. L., Amaro, C. M., Murray, C. B., & Holmbeck, G. N. (2015). Longitudinal study of neuropsychological functioning and internalizing symptoms in youth with spina bifida: social competence as a mediator. *Journal of pediatric psychology, 40*(3), 336–348.

Mahone, E. M., Martin, R., Kates, W. R., Hay, T., & Horská, A. (2009). Neuroimaging correlates of parent ratings of working memory in typically developing children. *Journal of the International Neuropsychological Society : JINS, 15*(1), 31–41.

Mak, M., Tyburski, E., Madany, Ł., Sokołowski, A., & Samochowiec, A. (2016). Executive Function Deficits in Patients after Cerebellar Neurosurgery. *Journal of the International Neuropsychological Society : JINS, 22*(1), 47–57.

Mammarella, N., Cornoldi, C., & Donadello, E. (2003). Visual but not spatial working memory deficit in children with spina bifida. *Brain and cognition, 53*(2), 311–314.

Mardia, K. V. (1974). Applications of Some Measures of Multivariate Skewness and Kurtosis in Testing Normality and Robustness Studies. *Sankhyā: The Indian Journal of Statistics, Series B (1960-2002), 36*(2), 115–128.

Mecklin, C. J., & Mundfrom, D. J. (2005). A Monte Carlo comparison of the Type I and Type II error rates of tests of multivariate normality. *Journal of Statistical Computation and Simulation, 75*(2), 93–107.

Meoded, A., Bosemani, T., Boltshauser, E., Scheer, I., Huisman, T.A.G.M., & Poretti, A. (2017). Diffusion Tensor Imaging and Fiber Tractography of Pediatric Posterior Fossa Malformations. *Neurographics, 7*(4), 243–261.

Miville, M. L., & Constantine, M. G. (2006). Sociocultural predictors of psychological help-seeking attitudes and behavior among Mexican American college students. *Cultural diversity & ethnic minority psychology, 12*(3), 420–432.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cognitive psychology, 41*(1), 49–100.

Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H., et al. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences of the United States of America, 108*(7), 2693–2698.

Nakatsu, T., Uwabe, C., & Shiota, K. (2000). Neural tube closure in humans initiates at multiple sites: evidence from human embryos and implications for the pathogenesis of neural tube defects. *Anatomy and embryology, 201*(6), 455–466.

O'Hara, L. K., & Holmbeck, G. N. (2013). Executive functions and parenting behaviors in association with medical adherence and autonomy among youth with spina bifida. *Journal of pediatric psychology, 38*(6), 675–687.

O'Reilly, J. X., Beckmann, C. F., Tomassini, V., Ramnani, N., & Johansen-Berg, H. (2010). Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. *Cerebral cortex (New York, N.Y. : 1991), 20*(4), 953–965.

Pierson, R., Corson, P. W., Sears, L. L., Alicata, D., Magnotta, V., Oleary, D., & Andreasen, N. C. (2002). Manual and semiautomated measurement of cerebellar subregions on MR images. *NeuroImage, 17*(1), 61–76.

Rencher, A.C., & Christensen, W.F. (2012). Multivariate Multiple Regression. In A.C. Rencher & W.F. Christensen (Eds.), *Methods of Multivariate Analysis* (pp. 338-383). Hoboken, New Jersey: John Wiley & Sons, Inc.

Rose, B. M., & Holmbeck, G. N. (2007). Attention and executive functions in adolescents with spina bifida. *Journal of pediatric psychology, 32*(8), 983–994.

Salmi, J., Pallesen, K. J., Neuvonen, T., Brattico, E., Korvenoja, A., Salonen, O., & Carlson, S. (2010). Cognitive and motor loops of the human cerebro-cerebellar system. *Journal of cognitive neuroscience, 22*(11), 2663–2676.

Schick, R. W., & Matson, D. D. (1961). What is arrested hydrocephalus? *The Journal of pediatrics, 58*, 791–799.

Sektnan, M., McClelland, M. M., Acock, A., & Morrison, F. J. (2010). Relations between early family risk, children's behavioral regulation, and academic achievement. *Early Childhood Research Quarterly, 25*(4), 464–479.

Sherman, L. E., Rudie, J. D., Pfeifer, J. H., Masten, C. L., McNealy, K., & Dapretto, M. (2014). Development of the default mode and central executive networks across early adolescence: a longitudinal study. *Developmental cognitive neuroscience, 10*, 148–159.

Stevenson, K. L. (2004). Chiari Type II malformation: past, present, and future. *Neurosurgical focus, 16*(2), E5.

Tang, T. L.-P., & Kim, J. K. (1999). The Meaning of Money among Mental Health Workers: The Endorsement of Money Ethic as Related to Organizational Citizenship Behavior, Job Satisfaction, and Commitment. *Public Personnel Management, 28*(1), 15–26.

Thorndike, R., Hagen, E., & Sattler, J. (1986). The Stanford-Binet intelligence scale. Itasca, IL: Riverside.

Verbruggen, F., & Logan, G. D. (2008). Response inhibition in the stop-signal paradigm. *Trends in cognitive sciences, 12*(11), 418–424.

Vinck, A., Maassen, B., Mullaart, R., & Rotteveel, J. (2006). Arnold-Chiari-II malformation and cognitive functioning in spina bifida. *Journal of neurology, neurosurgery, and psychiatry, 77*(9), 1083–1086.

Ware, A. L., Kulesz, P. A., Williams, V. J., Juranek, J., Cirino, P. T., & Fletcher, J. M. (2016). Gray matter integrity within regions of the dorsolateral prefrontal cortical-subcortical network predicts executive function and fine motor dexterity in spina bifida. *Neuropsychology, 30*(4), 492–501.

Wasserman, R. M., & Holmbeck, G. N. (2016). Profiles of Neuropsychological Functioning in Children and Adolescents with Spina Bifida: Associations with Biopsychosocial Predictors and Functional Outcomes. *Journal of the International Neuropsychological Society: JINS, 22*(8), 804–815.

Yeates, K. O., Loss, N., Colvin, A. N., & Enrile, B. G. (2003). Do children with myelomeningocele and hydrocephalus display nonverbal learning disabilities? An empirical approach to classification. *Journal of the International Neuropsychological Society: JINS, 9*(4), 653–662.

Zukerman, J. M., Devine, K. A., & Holmbeck, G. N. (2011). Adolescent predictors of emerging adulthood milestones in youth with spina bifida. *Journal of pediatric psychology, 36*(3), 265–276.